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HISTOPLASMOSIS

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Histoplasmosis is a fungal disease caused by *Histoplasma capsulatum*. *Histoplasma capsulatum* var *capsulatum* is a dimorphic fungus. In soil, it grows as a spore-bearing mold with macroconidia, but it converts to a yeast phase at body temperature.

Epidemiology

The quantity of inoculum inhaled, strain virulence, and the immune status of the host affect the degree of illness. Reinfection is possible but requires a large inoculum.

Histoplasmosis is not transmitted from person to person.

Occupational risk

Anyone working at a job or present near activities where material contaminated with *H. capsulatum* becomes airborne can develop histoplasmosis if enough spores are inhaled. After an exposure, how ill a person becomes varies greatly and most likely depends on the number of spores inhaled and a person's age and susceptibility to the disease. The number of inhaled spores needed to cause disease is unknown. Infants, young children, and older persons, in particular those with chronic lung disease, are at increased risk for developing symptomatic histoplasmosis.

Histoplasma in the environment

H. capsulatum grows in soils throughout the world. In the United States, the fungus is endemic and the proportion of people infected by *H. capsulatum* is higher in central and eastern states, especially along the valleys of the Mississippi, including Louisiana.

The fungus seems to grow best in soils having a high nitrogen content, especially those enriched with bird manure or bat droppings. The organism can be carried on the wings, feet, and beaks of birds and infect soil under roosting sites or manure accumulations inside or outside buildings. Active and inactive roosts of blackbirds (e.g., starlings, grackles, red-winged blackbirds, and cowbirds) have been found heavily contaminated by *H. capsulatum*. Therefore, the soil in a stand of trees where blackbirds have roosted for 3 or more years should be suspected of being contaminated by the fungus. Habitats of pigeons and bats, and poultry houses with dirt floors have also been found contaminated by *H. capsulatum*.

On the other hand, fresh bird droppings on surfaces such as sidewalks and windowsills have not been shown to present a health risk for histoplasmosis because birds themselves do not appear to be infected by *H. capsulatum*. Rather, bird manure is primarily a nutrient source for the growth of *H. capsulatum* already present in soil. Unlike birds, bats can become infected with *H. capsulatum* and consequently can excrete the organism in their droppings.

To learn whether soil or droppings are contaminated with *H. capsulatum* spores, samples must be collected and cultured. The culturing process involves inoculating mice with small portions of a sample, sacrificing the mice after 4 weeks, and streaking agar plates with portions of each mouse's liver and

spleen. Then for four more weeks, the plates are watched for the growth of *H. capsulatum*. Enough samples must be collected so that small but highly contaminated areas are not overlooked. On several occasions, *H. capsulatum* has not been recovered from any of the samples collected from material believed responsible for causing illness in people diagnosed from the results of clinical tests as having histoplasmosis.

Until a less expensive and more rapid method is available, testing field samples for *H. capsulatum* will be impractical in most situations. Consequently, when thorough testing is not done, the safest approach is to assume that the soil in regions where *H. capsulatum* is endemic and any accumulations of bat droppings or bird manure are contaminated with *H. capsulatum* and to take appropriate exposure precautions.

The incubation period is variable but usually is 1 to 3 weeks from the time of exposure.

Clinical Description

Less than 5% of infected persons are symptomatic. Clinical manifestations may be classified according to site (pulmonary, extrapulmonary, or disseminated), duration of infection (acute, chronic), and pattern of infection (primary vs reactivation).

Acute pulmonary histoplasmosis is an influenza-like illness with nonpleuritic chest pain, pulmonary infiltrates, and hilar adenopathy; symptoms persist for 2 or 3 days to 2 weeks. Erythema nodosum can occur in adolescents, but erythema nodosum and chronic pulmonary histoplasmosis are uncommon in children.

Primary cutaneous infections can occur after trauma.

Acute disseminated histoplasmosis is most frequent in children with impaired cell-mediated immunity, including patients with human immunodeficiency virus (HIV) infection and solid-organ transplant recipients, and infants younger than 1 year of age. Features include prolonged fever, failure to thrive, cough, hepatosplenomegaly, adenopathy, pneumonia, skin lesions, and pancytopenia. Central nervous system (CNS) involvement is common.

Chronic disseminated infection is rare. Histoplasmosis may reactivate years after primary infection in isolated tissues, particularly in the CNS, adrenal glands, and mucocutaneous surfaces, as well as in other sites.

Disseminated or extrapulmonary histoplasmosis is an acquired immunodeficiency syndrome–defining condition in an HIV-infected person.

Laboratory Tests

- Presence of organism on Giemsa or Wright stained smears of ulcers exudates, bone marrow, sputum, or blood (Not available at the State Laboratory).
- Culture on Sabouraud agar
- Biopsies of tissues (ulcers, liver, lymph nodes or lung) need special stains (Not available at the State Laboratory)
- Histoplasmin skin test (Not available at the State Laboratory).
- Serologic tests: immunodiffusion and CF titers in paired sera (Not available at the State Laboratory;
- Histoplasma antibodies (H & M bands) testing available in limited cases, with prior approval, through CDC).

Histoplasmosis can be diagnosed by identifying *H. capsulatum* in clinical samples of a symptomatic person's tissues or secretions, testing the patient's blood serum for antibodies to the microorganism, and

testing urine, serum, or other body fluids for *H. capsulatum* antigen. On occasion, diagnosis may require a transbronchial biopsy.

Culturing clinical specimens is a gold standard method of microbial identification, but the culturing process for isolating *H. capsulatum* is costly and time-consuming (2-6 weeks). To complicate matters, positive results are seldom obtained during the acute stage of the illness, except from clinical specimens from patients with disseminated histoplasmosis. A DNA probe for *H. capsulatum* significantly shortens the time required for identification in cultures. This procedure can be applied to nonsporulating cultures, thereby reducing the risk of exposure of laboratory personnel to infectious spores. Culture is done on Sabouraud agar from ulcers exudates, bone marrow, sputum, or blood (Not available at the State Laboratory).

Research advances in polymerase chain reaction (PCR) technology suggest that a laboratory method may soon be available that will allow direct identification of pathogenic fungi in clinical samples without the need for culturing them.

Direct demonstration of intracellular yeast by Gomori methenamine silver or other stains in smears of bone marrow or biopsy material from infected tissues is helpful for diagnosing disseminated or chronic histoplasmosis.

Most cases of histoplasmosis are diagnosed serologically. Because of their convenience, availability, and utility, the most widely accepted serologic tests are the immunodiffusion test and the complement-fixation test. Serologic test results are useful when positive. However, sometimes test results are negative even when a person is sick with histoplasmosis, a situation that arises especially in patients with weakened immune systems.

The immunodiffusion test qualitatively measures precipitating antibodies (H and M precipitin lines or bands) to concentrated histoplasmin. While this test is more specific for histoplasmosis (i.e., a person who is not infected with *H. capsulatum* is unlikely to have a positive test result) than the complement-fixation test, it is less sensitive (i.e., someone who is acutely infected can have a negative test result). Because the H band of the immunodiffusion test is usually present for only 4 to 6 weeks after exposure, it indicates active infection. The M band is observed more frequently, appears soon after infection, and may persist up to 3 years after a patient recovers.

The complement-fixation test, which measures antibodies to the intact yeast form and mycelial (histoplasmin) antigen, is more sensitive but less specific than the immunodiffusion test. Complement-fixing antibodies may appear in 3 to 6 weeks (sometimes as early as 2 weeks) following infection by *H. capsulatum*, and repeated tests will give positive results for months. The results of complement-fixation tests are of greatest diagnostic usefulness when both acute and convalescent serum specimens can be obtained. A high titer (1:32 or higher) or a fourfold increase is indicative of active histoplasmosis. Lower titers (1:8 or 1:16), although less specific, may also provide presumptive evidence of infection, but they can also be measured in the serum of healthy persons from regions where histoplasmosis is endemic. Antibody titers will gradually decline and eventually disappear months to years after a patient recovers.

A person can learn from a histoplasmin skin test whether he or she has been previously infected by *H. capsulatum*. This test, similar to a tuberculin skin test, is available at many physicians' offices and medical clinics. A histoplasmin skin test becomes positive 2 to 4 weeks after a person is infected by *H. capsulatum*, and repeated tests will usually give positive results for the rest of the person's life. A previous infection by *H. capsulatum* can provide partial protection against ill effects if a person is reinfected. Since a positive skin test does not mean that a person is completely protected against ill effects, appropriate exposure precautions should be taken regardless of a worker's skin-test status. Furthermore, while histoplasmin skin test information is useful to epidemiologists, a positive skin test does not help diagnose acute histoplasmosis, unless a previous skin test is known to have been negative.

A radioimmunoassay method can be used to measure *H. capsulatum* polysaccharide antigen (HPA) levels in samples of a patient's urine, serum, and other body fluids. The test appears to meet the important need for a rapid and accurate method for early diagnosis of disseminated histoplasmosis, especially in patients with AIDS. HPA is detected in body fluid samples of most patients with disseminated infection and in the urine and serum of 25% to 50% of those with less severe infections. Cross-reacting antigens have been detected in persons with disseminated infection due to blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei*.

Treatment

Immunocompetent children with uncomplicated, primary pulmonary histoplasmosis rarely require antifungal therapy. Indications for therapy include progressive disseminated infection in infants and acute infection in immunocompromised patients. Other manifestations of histoplasmosis in immunocompetent children for which antifungal therapy should be considered include pulmonary disease with symptoms persisting more than 4 weeks, seriously ill patients with intense exposures, and adenopathy that obstructs critical structures (ie, bronchi, blood vessels).

Amphotericin B is effective and recommended for disseminated disease. In other circumstances in which antifungal therapy is warranted, itraconazole and fluconazole also have been effective. The safety and efficacy of itraconazole for use in children have not been established, but in adults, itraconazole is preferred over fluconazole and has negligible toxic effects. Itraconazole also has proven effective in the treatment of mild disseminated histoplasmosis in HIV-infected patients.

The duration of treatment for disseminated disease with amphotericin B is 4 weeks except in HIV-infected patients. Mild infections in HIV-infected patients can be treated with itraconazole for 3 months; moderate or severe infections should be treated with 2 weeks of amphotericin B followed by 10 weeks of itraconazole. Patients with HIV infection require lifelong suppressive therapy with itraconazole or, if not tolerated, fluconazole.

Surveillance

Histoplasmosis is not a reportable condition unless outbreaks are observed.

Case Definition

A case of histoplasmosis is an illness characterized by an acute or chronic pulmonary syndrome and laboratory confirmation of the presence of *H.capsulatum*.

Investigation

No routine investigation of cases is necessary for sporadic cases. However questions often come up for advice on exposure, health effects and prevention.

Hospital precaution and isolation: Standard precautions

Prevention of transmission for workers

The U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) have jointly published guidelines for the prevention of opportunistic infections in persons infected with the human immunodeficiency virus (HIV). The USPHS/IDSA Prevention of Opportunistic Infections Working Group recommended that HIV-infected persons "should avoid activities known to be associated with increased risk (e.g., cleaning chicken coops, disturbing soil beneath bird-roosting sites, and exploring

caves). HIV-infected persons should consult their health care provider about appropriate exposure precautions that should be taken for any activity with a risk of exposure to *H. capsulatum*. Below is a partial list of occupations and hobbies with risks for exposure to *H. capsulatum* spores. Appropriate exposure precautions should be taken by these people and others whenever contaminated soil, bat droppings, or bird manure are disturbed.

- Bridge inspector or painter
- Chimney cleaner
- Construction worker
- Demolition worker
- Farmer
- Gardener
- Heating and air-conditioning system installer or service person
- Microbiology laboratory worker
- Pest control worker
- Restorer of historic or abandoned buildings
- Roofer
- Spelunker (cave explorer)

If someone who engages in these activities develops flu-like symptoms days or even weeks after disturbing material that might be contaminated with *H. capsulatum*, and the illness worsens rather than subsides after a few days, medical care should be sought and the health care provider informed about the exposure.

Pre-exposure skin tests

Workers at risk of exposure to *H. capsulatum* may learn useful information from a histoplasmin skin test. The results of skin testing would inform each worker of his or her status regarding either susceptibility to infection by *H. capsulatum* (a negative skin test) or partial protection against ill effects if reinfected (a positive skin test). However, a false-negative skin test result can be reported early in an infection or with persons with weakened immune systems. A false-positive skin test can result from cross-reactions with antigens of certain other pathogenic fungi. One drawback to routine pre-exposure skin testing is that a person with a positive skin test might incorrectly assume a false sense of security that he or she is completely protected against ill effects if reinfected. The work practices and personal protective equipment described in this booklet are expected to protect both skin-test positive and skin-test negative persons from excessive inhalation exposures to materials that might be contaminated with *H. capsulatum*. Although a pre-exposure serum sample could be useful in determining whether a worker's post-exposure illness is histoplasmosis, routine collection and storage of serum specimens from workers is unnecessary and impractical in most work settings. Some employers, such as public health agencies and microbiology laboratories, have facilities for long-term storage of serum and do collect pre-exposure serum specimens from those employees who might be exposed to high-risk infectious agents. If a worker is to have blood drawn for this purpose and is to receive a histoplasmin skin test, the blood sample should be drawn first because the skin test may cause a positive complement-fixation test for up to 3 months and the appearance of the M band on an immunodiffusion test for *H. capsulatum*.

Reducing exposures to *H. capsulatum*

Excluding a colony of bats or a flock of birds from a building

The best work practice is to prevent the accumulation of manure in the first place. Therefore, when a colony of bats or a flock of birds is discovered roosting in a building, immediate action should be taken to exclude the intruders by sealing all entry points. Any measure that might unnecessarily harm or kill a bat or bird should be avoided.

Before excluding a colony of bats or a flock of birds from a building, attention should be given to the possibility that flightless young may be present. In the United States, this is an especially important consideration for bats from May through August. Ultrasonic devices and chemical repellents are ineffective for eliminating bats from a roosting area. While there may be several openings in a building, bats will typically use only one or two. Therefore, after observing the bats leaving a building on several nights, all openings except the ones used by the bats should be sealed. Because some bats are so small that they can squeeze through an opening smaller than the diameter of a dime, even the smallest hole should be sealed. Exclusion valves – flaps made of polypropylene bird netting that allow bats to leave but not enter – should then be placed over the remaining openings. If these openings are inaccessible, installing and maintaining lights in a roosting area will force bats to seek another daytime roosting site. Because of concerns for the welfare of evicted bats, constructing bat houses near former roosts has become a common practice of some pest control companies.

In some buildings, extensive bat exclusion measures may be more successful in the late fall or winter months after a colony has migrated to a warmer habitat or to another location for hibernation. In some regions of the United States, bats may not migrate, but rather will hibernate in the same building. Consequently, any work on a building that might disturb such a colony should be delayed until spring. Disturbing bats during hibernation is likely to result in their death.

Excluding birds from a building also involves sealing entry points. Because their food source is usually nearby, birds prevented from reentering a building will often complicate an exclusion by beginning to roost on window sills and ledges of the building or others nearby. Visual deterrents (e.g., balloons, flags, lights, and replicas of hawks and owls) and noises (e.g., gun shots, alarms, gas cannons, and fireworks) may scare birds away, but generally only temporarily.

Nontoxic, chemical bird repellents are available as liquids, aerosols, and nondrying films and pastes. Disadvantages of these antiroosting materials are that some are messy and none are permanent. Even the most effective ones require periodic reapplication. More permanent repellents include mechanical antiroosting systems consisting of angled and porcupine wires made of stainless steel. These systems may require some occasional maintenance to clear nesting material or other debris from the wires.

Live trapping of birds to relocate them is seldom effective when traps are put in a roosting site, but this method can be effective when used in a feeding area. Shooting birds, using contact poisons, and baiting with poisoned food should be used as last resorts and should only be done by qualified pest control specialists. Using such methods to kill nuisance birds may also require a special permit.

Posting health risk warnings

If a colony of bats or a flock of birds is allowed to live in a building or a stand of trees, their manure will accumulate and create a health risk for anyone who enters the roosting area and disturbs the material. Once a roosting site has been discovered in a building, exclusion plans should be made, and the extent of contamination should be determined. When an accumulation of bat or bird manure is discovered in a building, removing the material is not always the next step. Simply leaving the material alone if it is in a location where no human activity is likely may be the best course of action.

Areas known or suspected of being contaminated by *H. capsulatum*, such as bird roosts, attics, or even entire buildings that contain accumulations of bat or bird manure, should be posted with signs warning of the health risk. Each sign should provide the name and telephone number of a person to be contacted if there are questions about the area. In some situations, a fence may need to be built around a property or locks put on attic doors to prevent unsuspecting or unprotected individuals from entering.

Communicating health risks to workers

Before an activity is started that may disturb any material that might be contaminated by *H. capsulatum*, workers should be informed in writing of the personal risk factors that increase an individual's chances of developing histoplasmosis. Such a written communication should include a warning that individuals with weakened immune systems are at the greatest risk of developing severe and disseminated histoplasmosis if they become infected. These people should seek advice from their health care provider about whether they should avoid exposure to materials that might be contaminated with *H. capsulatum*.

Controlling aerosolized dust when removing bat or bird manure from a building

The best way to prevent exposure to *H. capsulatum* spores is to avoid situations where material that might be contaminated can become aerosolized and subsequently inhaled. A brief inhalation exposure to highly contaminated dust may be all that is needed to cause infection and subsequent development of histoplasmosis. Therefore, work practices and dust control measures that eliminate or reduce dust generation during the removal of bat or bird manure from a building will also reduce risks of infection and subsequent development of disease. For example, instead of shoveling or sweeping dry, dusty material, carefully wetting it with a water spray can reduce the amount of dust aerosolized during an activity. Adding a surfactant or wetting agent to the water might reduce further the amount of aerosolized dust. Once the material is wetted, it can be collected in double, heavy-duty plastic bags, a 55-gallon drum, or some other secure container for immediate disposal. An alternative method is use of an industrial vacuum cleaner with a high-efficiency filter to *bag* contaminated material. Truck-mounted or trailer-mounted vacuum systems are recommended for buildings with large accumulations of bat or bird manure. These high-volume systems can remove tons of contaminated material in a short period. Using long, large-diameter hoses, such a system can also remove contaminated material located several stories above its waste hopper. This advantage eliminates the risk of dust exposure that can happen when bags tear accidentally or containers break during their transfer to the ground.

The removal of all material that might be contaminated by *H. capsulatum* from a building and immediate waste disposal will eliminate any further risk that someone might be exposed to aerosolized spores. Air sampling, surface sampling, or the use of any other method intended to confirm that no infectious agents remain following removal of bat or bird manure is unnecessary in most cases. However, before a removal activity is considered finished, the cleaned area should be inspected visually to ensure that no residual dust or debris remains.

Disinfecting contaminated material

Disinfectants have occasionally been used to treat contaminated soil and accumulations of bat manure when removal was impractical or as a precaution before a removal process was started. Formaldehyde solutions are the only disinfectants proven to be effective for decontaminating soil containing *H. capsulatum*. Because of the potentially serious health hazards associated with formaldehyde exposures, this chemical should be handled only by persons who know how to apply it safely. If a disinfectant is applied to land known to be contaminated by *H. capsulatum*, the soil should be thoroughly saturated so that the disinfectant penetrates deeply enough to contact all the soil containing *H. capsulatum*. While *H. capsulatum* was found in a blackbird roost at a depth of more than 12 inches, soil saturation to a depth of 6 to 8 inches will be sufficient for most disinfectant applications. To ensure a disinfectant's effectiveness, soil samples should be collected before and after an application and analyzed for *H. capsulatum*. The appropriate number of samples to be collected will vary depending upon the size of the property. Each sampling location should be flagged or marked in a way that will ensure that the same locations will be sampled after application of the disinfectant. A map of the treated area showing the approximate location of each sampling site will also be useful in the event flags or markings are lost. After a disinfectant's effectiveness has been documented – more than one application may be necessary – additional tests for *H. capsulatum* should be done periodically if the land remains idle.

Disposing of waste

Any material that might be contaminated with *H. capsulatum* that is removed from a work site should be disposed of or decontaminated properly and safely and not merely moved to another area where it could still be a health hazard. Before an activity is started, the quantity of material to be removed should be estimated. (If the approximate volume of dry bat or bird manure in a building is known, the approximate weight can be calculated using a conversion factor of 40 pounds per cubic foot.) Requirements established by local and state authorities for the removal, transportation, and disposal of contaminated material should be followed. Arrangements should be made with a landfill operator concerning the quantity of material to be disposed of, the dates when the material will be delivered, and the disposal location. If local or state landfill regulations define material contaminated with *H. capsulatum* to be infectious waste, incineration or another decontamination method may also be required.

Controlling aerosolized dust during construction, excavation, and demolition

Dusts containing *H. capsulatum* spores can be aerosolized during construction, excavation, or demolition. Once airborne, spores can be carried easily by wind currents over long distances. Such contaminated airborne dusts can cause infections not only in persons at a work site, but also in others nearby. Such activities were suggested as the causes of the three largest outbreaks of histoplasmosis ever recorded. All three outbreaks took place in Indianapolis, Indiana. During the first outbreak, in the fall of 1978 and spring of 1979, an estimated 120,000 people were infected, and 15 people died. The second outbreak, in 1980, was similar to the first in the number of people affected. AIDS patients accounted for nearly 50% of culture-proven cases during the third outbreak, in 1988.

Water sprays or other dust suppression techniques should be used to reduce the amount of dust aerosolized during construction, excavation, or demolition in regions where *H. capsulatum* is endemic. During windy periods or other times when typical dust suppression techniques are ineffective, earthmoving activities should be interrupted. All earthmoving equipment (e.g., bulldozers, trucks, and front-end loaders) should have cabs with air-conditioning (if available) to protect their operators. Air filters on air-conditioners should be inspected on a regular schedule and cleaned or replaced as needed. During filter cleaning or replacement of exceptionally dusty air filters, respiratory protection should be worn by the maintenance person if there is a potential for the dust to be aerosolized. Beds of all trucks carrying dirt or debris from a work site should be covered, and all trucks should pass through a wash station before leaving the site. When at a dump site, a truck operator should ensure that all individuals in the vicinity are in an area where they will not be exposed to dust aerosolized while the truck is emptied. Water sprays and other suppression techniques may not be enough to control dust aerosolized during demolition of a building or other structure. Consequently, removal of accumulations of bird or bat manure before demolition may be necessary in some situations. Factors affecting decisions about pre-demolition removal of such accumulations include the quantity and locations of the material, the structural integrity or soundness of the building, weather conditions, proximity of the building to other buildings and structures, and whether nearby buildings are occupied by persons who may be at increased risk for developing symptomatic histoplasmosis (e.g., schools, day-care facilities, hospitals, clinics, jails, and prisons).

City or county governments in regions where *H. capsulatum* is endemic should establish and enforce regulations concerning work practices that will control dust aerosolization at construction, excavation, and demolition sites. However, even in regions where *H. capsulatum* is not considered endemic, dust aerosolized during work activities in bird roosts has also resulted in outbreaks of histoplasmosis. Consequently, regardless of whether a work site is in an endemic region, precautions should be taken at active and inactive bird roosts to prevent dust aerosolization.

Wearing personal protective equipment

Because work practices and dust control measures to reduce worker exposures to *H. capsulatum* have not been fully evaluated, using personal protective equipment is still necessary during some activities. During removal of an accumulation of bat or bird manure from an enclosed area such as an attic, dust control measures should be used, but wearing a NIOSH-approved respirator and other items of personal protective equipment is also recommended to reduce further the risk of *H. capsulatum* exposure.

For some jobs involving exposures to airborne dusts, working conditions have changed little over the years despite improvements in other aspects of the industry. For example, inhalation of dust aerosolized from the dirt floors of chicken coops that contained *H. capsulatum* spores was reported more than 30 years ago as the cause of clinical cases of histoplasmosis in workers. As the poultry industry has grown (there are now approximately 120,000 poultry farms in the United States), the old-style chicken coop has been replaced by larger housing facilities. However, the floors of poultry houses are still dirt covered and provide an excellent medium for the growth of *H. capsulatum*. Ventilation systems in poultry houses are not primarily intended to reduce poultry workers' exposures to aerosolized dust, and dust measurements made during growing and catching chickens show that inhalation exposures of poultry workers to dust can be excessive. Since ventilation systems designed especially to reduce airborne dust to "safe" levels in poultry houses would likely be economically and mechanically impractical, wearing a respirator is probably the most feasible method for protecting poultry workers.